



Dkt. 1919/62814-A/JPW/GJG/MML

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Timothy Norris et al.

Serial No. : 09/711,272

GROUP ART UNIT: 1624

Filed : November 9, 2000

EXAMINER: T. McKenzie

For : STABLE POLYMORPH ON N-(3-ETHYNYLPHENYL)-6, 7-BIS
(2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE,
METHODS OF PRODUCTION, AND PHARMACEUTICAL USES
THEREOF

1185 Avenue of the Americas
New York, New York 10036
July 22, 2004

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

COMMUNICATION UNDER 37 C.F.R. §1.312

A Notice of Allowance was issued on May 26, 2004 in connection with the above-identified application indicating that it was responsive to applicants' RCE of September 18, 2003. However, applicants also filed a Second Supplemental Amendment in connection with this application on December 15, 2003, a copy of which is attached as **Exhibit A**. The May 26, 2004 Notice of Allowability which accompanied the Notice of Allowance did not indicate that applicants' December 15, 2003 Amendment has been entered and considered.

Applicants hereby request pursuant to 37 C.F.R. §1.312 that their December 15, 2003 Second Supplemental Amendment be entered and considered in the above-identified application. As evidence of receipt of the December 15, 2003 Amendment by the United States Patent and Trademark Office, applicants also

include in **Exhibit A** a copy of the facsimile receipt confirmation generated by the Office on December 15, 2003.

In addition, applicants request that the Examiner confirm that certain references which were not initialed by the Examiner have been considered. Specifically, in the copies of the PTO Form 1449 attached to the May 26, 2004 Notice of Allowability, the following four references were not initialed:

1. U.S. Patent Application Publication No. 2002/0061304, Miller et al., published May 23, 2002 (**Exhibit 1**);
2. U.S. Patent No. 6,476,040, Norris et al., issued November 5, 2002 (**Exhibit 2**);
3. U.S. Patent No. 6,169,091, Cockerill et al., issued January 2, 2001 (**Exhibit 3**); and
4. U.S. Application Serial No. 09/355,534, Allen et al., filed July 29, 1999, **claims only** (3 pages) (**Exhibit 4**).

Applicants note that item 4 is a copy of what were the pending claims of copending U.S. Application Serial No. 09/355,534 ("the '534 application"). The pending claims of the '534 application were submitted for the Examiner's consideration pursuant to 37 C.F.R. §1.98(a). The '534 application is a §371 national stage of PCT International Application PCT/IB99/00612, which published on November 4, 1999 as WO 99/55683. WO 99/55683 was submitted by applicants in an Information Disclosure Statement filed June 29, 2001 and has been considered by the Examiner in this application. Applicants further note that the '534 application issued on March 16, 2004 as U.S. Patent No. 6,706,721 ("the '721 patent"). A copy of the '721 patent is enclosed as **Exhibit 5** for the Examiner's consideration. Applicants request that the

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Examiner make this patent of record in the subject application. A form PTO 1449 listing the '721 patent and again listing U.S. Serial No. 09/355,534 (claims only, 3 pages) is attached as **Exhibit B**.

Applicants also note that item 2 was cited by the Examiner on Form PTO-892 attached to the Notice of Allowability. However, for completeness of the record, applicants request that the Examiner also initial item 2 on the Form PTO 1449.

During a July 21, 2004 telephone conference between Examiner McKenzie and Muriel Liberto of the undersigned attorney's office, Examiner McKenzie indicated that the December 15, 2003 Amendment was not considered due to an error on the part of the Patent Office and that the Amendment would be considered upon the filing of a request pursuant to 37 C.F.R. §1.312.

Examiner McKenzie further stated that he would initial all considered references submitted in applicants' Supplemental Information Disclosure Statements of September 30, 2003 and September 18, 2003. In order to facilitate the Examiner's consideration of these references, copies of items 1-4 are attached hereto as **Exhibits 1-4**, respectively. Copies of the partially initialed PTO Forms 1449 are attached hereto as **Exhibit C** (2 pages). Applicants respectfully request that the Examiner consider items 1-4 and return a copy of each completely initialed PTO Form 1449 to applicants.

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No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.


Respectfully submitted,



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MESSAGE: Re: U.S. Serial No. 09/711,272

SECOND SUPPLEMENTAL AMENDMENT in connection with Timothy Morris et al. STABLE POTYMORPH OF N-(3-ETHYNYLPHENYL)-6, 7-BIS (2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE. METHODS OF PRODUCTION, AND PHARMACEUTICAL USES THEREOF

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Timothy Norris et al.
Serial No. : 09/711,272 Group Art Unit: 1624
Filed : November 9, 2000 Examiner: T. McKenzie
For : STABLE POLYMORPH ON N-(3-ETHYNYLPHENYL)-6,
7-BIS (2-METHOXYETHOXY)-4-QUINAZOLINAMINE
HYDROCHLORIDE, METHODS OF PRODUCTION, AND
PHARMACEUTICAL USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
December 15, 2003

BY FACSIMILE - 703-872-9306

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

SECOND SUPPLEMENTAL AMENDMENT

A Request for Continued Examination ("RCE") including a Supplemental Amendment was filed on September 18, 2003 in connection with the above-identified application. Accordingly, this application is currently pending and this Amendment is being timely filed.

Please amend the subject application as follows:

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Amendments to the claims

Please cancel claims 73, 90 and 91 without prejudice to applicants' right to pursue the subject matter of these claims in this or a related application.

Please amend claims 26, 29, 50, 63, 64 , 71, 72 and 74, and add new claims 92-110 under the provisions of 37 C.F.R. §1.121, as set forth in the Federal Register on June 30, 2003 as follows:

1. (Previously amended) A homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14, and 26.91.
2. (Original) The polymorph of claim 1, characterized by the X-ray powder diffraction pattern shown in Figure 3.
3. (Previously amended) A crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph.
4. (Original) The polymorph of claim 3, characterized by the X-ray powder diffraction pattern shown in Figure 3.
5. (Previously amended) A composition comprising a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, and a carrier, wherein the composition is free of the A polymorph.

6. (Original) The composition of claim 5, wherein the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately:

| 2-Theta | I(rel) | 2-Theta | I(rel) | 2-Theta | I(rel) | 2-Theta | I(rel) | 2-Theta | I(rel) |
|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|
| 6.255 | 100.0 | 17.668 | 2.5 | 22.982 | 4.8 | 27.534 | 0.9 | 32.652 | 1.7 |
| 7.860 | 3.2 | 18.193 | 0.7 | 23.589 | 2.3 | 28.148 | 1.5 | 33.245 | 1.7 |
| 9.553 | 3.9 | 18.749 | 1.5 | 23.906 | 3.0 | 28.617 | 4.3 | 34.719 | 1.5 |
| 11.414 | 1.5 | 19.379 | 1.0 | 24.459 | 6.8 | 29.000 | 1.4 | 35.737 | 0.8 |
| 12.483 | 6.4 | 20.196 | 14.4 | 25.138 | 10.0 | 29.797 | 2.1 | 36.288 | 1.0 |
| 13.385 | 9.6 | 20.734 | 4.2 | 25.617 | 3.7 | 30.267 | 0.9 | 36.809 | 0.6 |
| 14.781 | 2.1 | 21.103 | 14.4 | 25.908 | 3.9 | 30.900 | 1.6 | 37.269 | 1.1 |
| 15.720 | 2.9 | 21.873 | 4.7 | 26.527 | 2.8 | 31.475 | 2.2 | 37.643 | 1.4 |
| 16.959 | 5.5 | 22.452 | 4.5 | 26.911 | 5.6 | 31.815 | 2.4 | 38.114 | 1.7 |

7. (Original) The composition of claim 5, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

Claims 8-13. (Canceled)

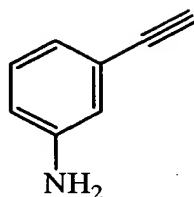
14. (Previously amended) A method of treating abnormal cell growth of a cell expressing the epidermal growth factor receptor (EGFR) in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim 3, wherein the abnormal cell growth is brain cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, glioblastoma multiforme breast cancer, head cancer, neck cancer, esophageal cancer, prostate cancer, colorectal cancer, lung cancer, renal cancer, kidney cancer, ovarian cancer, gynecological cancer, thyroid cancer, non-small cell lung

cancer (NSCLC), refractory ovarian cancer, or head and neck cancer.

15. (Previously amended) The method of claim 14, wherein the abnormal cell growth is brain, squamous cell, bladder, gastric, pancreatic, hepatic, glioblastoma multiforme breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological or thyroid cancer.
16. (Previously amended) The method of claim 14, wherein the abnormal cell growth is non-small cell lung cancer (NSCLC), refractory ovarian cancer, or head and neck cancer.
17. (Original) The method of claim 14, wherein the therapeutically effective amount is from about 0.001 to about 100 mg/kg/day.
18. (Original) The method of claim 14, wherein the therapeutically effective amount is from about 1 to about 35 mg/kg/day.
19. (Original) The method of claim 14, wherein the therapeutically effective amount is from about 1 to about 7000 mg/day.
20. (Original) The method of claim 19, wherein the therapeutically effective amount is from about 5 to about 2500 mg/day.
21. (Original) The method of claim 20, wherein the therapeutically effective amount is from about 5 to about 200 mg/day.

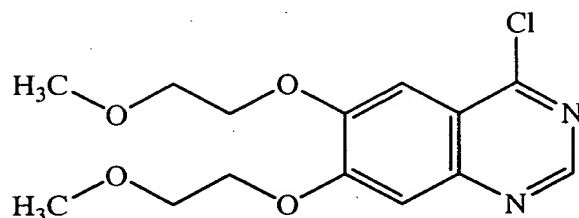
Applicants: Timothy Norris et al.
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22. (Original) The method of claim 21, wherein the therapeutically effective amount is from about 25 to about 200 mg/day.
23. (Previously amended) A method for the treatment of abnormal cell growth of a cell expressing the epidermal growth factor receptor (EGFR) in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim 3 in combination with an anti-tumor agent selected from the group consisting of a mitotic inhibitor, an alkylating agent, an anti-metabolite, an intercalating antibiotic, a growth factor inhibitor, a cell cycle inhibitor, an enzyme, a topoisomerase inhibitor, a biological response modifier, an anti-hormone, and an anti-androgen.
24. (Previously amended) A process for preparing a crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride designated the B polymorph, which is free of the A polymorph, which comprises the step of recrystallizing N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in a solvent comprising alcohol.
25. (Previously amended) The process of claim 24, wherein the solvent further comprises water.
26. (Currently Amended) The process of claim 24, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride is prepared by coupling a compound of formula



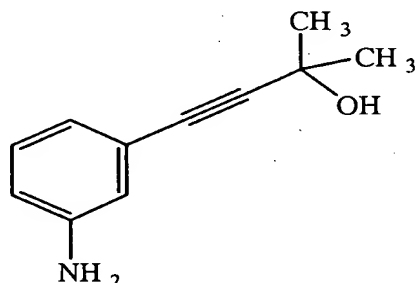
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with a compound of formula 4



4.

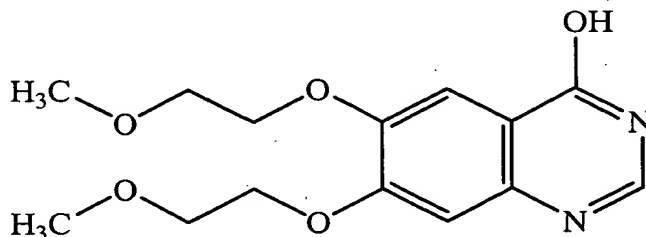
27. (Previously amended) The process of claim 26, wherein said compound of formula 6 is prepared by heating a compound of formula 5



5

in a suspension of metal alkali and solvent.

28. (Previously amended) The process of claim 26, wherein said compound of formula 4 is prepared by chlorinating a compound of formula 3

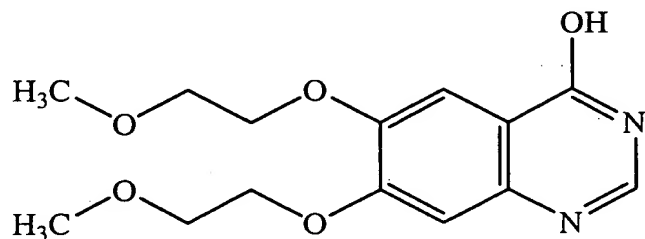


3.

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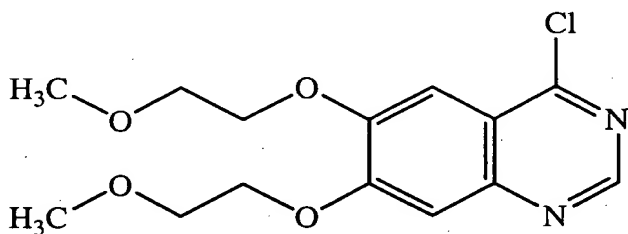
29. (Currently Amended) A process for the production of the polymorph B of claim 1 comprising the steps of:

a) substitution chlorination of ~~starting quinazolinamine~~ a compound of formula 3



3

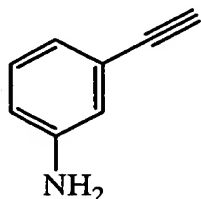
having an hydroxyl group, to provide a compound of formula 4



4

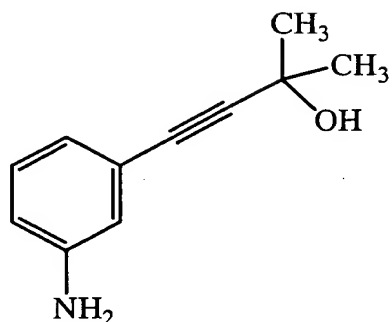
by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide;

b) preparation of a compound of formula 6



6

in situ from starting material of compound of formula 5



by heating the compound of formula 5 in a suspension of metal alkali and solvent;

c) reaction of the compound of formula 6 in situ with the compound of formula 4 wherein the compound of formula 6 replaces the chlorine in the compound of formula 4 to give the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride; and

d) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in alcohol, into the polymorph B form.

30. (Previously amended) The process of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous sodium hydroxide.
31. (Previously amended) The process of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous sodium bicarbonate.
32. (Previously amended) The process of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous potassium hydroxide, aqueous potassium bicarbonate, aqueous potassium carbonate, aqueous sodium carbonate, or a mixture thereof.

Claims 33-49. (Canceled)

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50. (Currently amended) A method of inhibiting the development of basal or squamous cell carcinoma of the skin in areas exposed to the sun or in persons of high risk to said carcinoma, said method comprising administering to said persons a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, ~~and pharmaceutically or pharmaceutically~~ acceptable salts thereof in anhydrous ~~and hydrate~~ or hydrate forms, and a carrier, so as to thereby inhibit the development of basal or squamous cell carcinoma of the skin.

Claim 51. (Canceled)

52. (Previously amended) A process of making a composition which composition comprises a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph, comprising admixing the crystalline polymorph with a carrier.

53. (Previously amended) The process of claim 52, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

54. (Previously amended) The process of claim 52, wherein the carrier is a pharmaceutically acceptable carrier.

Claims 55-57. (Canceled)

58. (Previously amended) A pharmaceutical composition which comprises a therapeutically effective amount of the polymorph of claim 3 and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is free of the A polymorph.
59. (Previously presented) The pharmaceutical composition of claim 58, wherein said composition is adapted for oral administration.
60. (Previously presented) The pharmaceutical composition of claim 59, wherein the pharmaceutical composition is in the form of a tablet.
61. (Previously amended) A process for the production of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph by recrystallization comprising the steps of:
- a) heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution;
 - b) cooling the solution to between about 65 and 70 °C;
 - c) clarifying the solution; and
 - d) precipitating polymorph B by further cooling the clarified solution.
62. (Previously amended) A composition consisting of a homogeneous crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in

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the form of polymorph B, which is characterized by the following peaks:

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)

Range # 1 - Coupled 3.000 to. 40.040 StepSize: 0.040 StepTime 1.00

Smoothing Width: 0.300 Threshold: 1.0

| d(A) | I(rel) | d(A) | I(rel) | d(A) | I(rel) | d(A) | I(rel) | d(A) | I(rel) |
|----------|--------|---------|--------|---------|--------|---------|--------|---------|--------|
| 14.11826 | 100.0 | 5.01567 | 2.5 | 3.86656 | 4.8 | 3.23688 | 0.9 | 2.74020 | 1.7 |
| 11.23947 | 3.2 | 4.87215 | 0.7 | 3.76849 | 2.3 | 3.16755 | 1.5 | 2.69265 | 1.7 |
| 9.25019 | 3.9 | 4.72882 | 1.5 | 3.71927 | 3.0 | 3.11673 | 4.3 | 2.58169 | 1.5 |
| 7.74623 | 1.5 | 4.57666 | 1.0 | 3.63632 | 6.8 | 3.07644 | 1.4 | 2.51043 | 0.8 |
| 7.08519 | 6.4 | 4.39330 | 14.4 | 3.53967 | 10.0 | 2.99596 | 2.1 | 2.47356 | 1.0 |
| 6.60941 | 9.6 | 4.28038 | 4.2 | 3.47448 | 3.7 | 2.95049 | 0.9 | 2.43974 | 0.6 |
| 5.98828 | 2.1 | 4.20645 | 14.4 | 3.43610 | 3.9 | 2.89151 | 1.6 | 2.41068 | 1.1 |
| 5.63253 | 2.9 | 4.06007 | 4.7 | 3.35732 | 2.8 | 2.83992 | 2.2 | 2.38755 | 1.4 |
| 5.22369 | 5.5 | 3.95667 | 4.5 | 3.31029 | 5.6 | 2.81037 | 2.4 | 2.35914 | 1.7 |

or,

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)

Range# 1 - Coupled: 3.000 to 40.040 StepSize 0.040 StepTime: 1.00

Soothing Width:0.300 Threshold: 1.0

| 2-Theta | I(rel) | 2-Theta | I(rel) | 2-Theta | I(rel) | 2-Theta | I(rel) | 2-Theta | I(rel) |
|---------|--------|---------|--------|---------|--------|---------|--------|---------|--------|
| 6.255 | 100.0 | 17.668 | 2.5 | 22.982 | 4.8 | 27.534 | 0.9 | 32.652 | 1.7 |
| 7.860 | 3.2 | 18.193 | 0.7 | 23.589 | 2.3 | 28.148 | 1.5 | 33.245 | 1.7 |
| 9.553 | 3.9 | 18.749 | 1.5 | 23.906 | 3.0 | 28.617 | 4.3 | 34.719 | 1.5 |
| 11.414 | 1.5 | 19.379 | 1.0 | 24.459 | 6.8 | 29.000 | 1.4 | 35.737 | 0.8 |
| 12.483 | 6.4 | 20.196 | 14.4 | 25.138 | 10.0 | 29.797 | 2.1 | 36.288 | 1.0 |
| 13.385 | 9.6 | 20.734 | 4.2 | 25.617 | 3.7 | 30.267 | 0.9 | 36.809 | 0.6 |
| 14.781 | 2.1 | 21.103 | 14.4 | 25.908 | 3.9 | 30.900 | 1.6 | 37.269 | 1.1 |
| 15.720 | 2.9 | 21.873 | 4.7 | 26.527 | 2.8 | 31.475 | 2.2 | 37.643 | 1.4 |
| 16.959 | 5.5 | 22.452 | 4.5 | 26.911 | 5.6 | 31.815 | 2.4 | 38.114 | 1.7 |

and at least one carrier.

63. (Currently amended) A method of treating a subject with a tumor by inducing differentiation of tumor cells expressing an epidermal growth factor receptor (EGFR) in the tumor comprising contacting the cells with an effective amount of the compound of claim 3, or a composition of ~~claim 5~~ claim 5, so as to thereby treat the subject, wherein the tumor is brain cancer, squamous cell cancer, bladder cancer, gastric

cancer, pancreatic cancer, hepatic cancer, glioblastoma multiforme breast cancer, head cancer, neck cancer, esophageal cancer, prostate cancer, colorectal cancer, lung cancer, renal cancer, kidney cancer, ovarian cancer, gynecological cancer, thyroid cancer, non-small cell lung cancer (NSCLC), refractory ovarian cancer, or head and neck cancer.

64. (Currently amended) A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), endometrial cancer, ~~glioma, melanoma,~~ Barrett's esophagus (pre-malignant syndrome), ~~adrenal cancers, or~~ neoplastic cutaneous diseases ~~or atherosclerosis~~ in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine ~~,and pharmaceutically or pharmaceutically~~ acceptable salts thereof in anhydrous and hydrate or hydrate forms, and a carrier.
65. (Previously presented) The method of claim 64, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.
66. (Previously presented) The method of claim 64, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).
67. (Previously presented) The method of claim 64, for use in treatment of tumors that express EGFRvIII.

68. (Previously presented) The method of claim 64, wherein the treatment further comprises a combination with any of chemotherapy and immunotherapy.
69. (Previously presented) The method of claim 64, wherein the treatment further comprises, treatment with either or both anti-EGFR and anti-EGF antibodies.
70. (Previously presented) The method of claim 64, wherein the treatment further comprises a further administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, CTLA₄ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab.
71. (Currently Amended) The method of claim 64, wherein the pharmaceutical ~~compounds are~~ composition is used as a radiation ~~sensitizers~~ sensitizer for cancer treatment or in combination with anti-hormonal therapies.
72. (Currently Amended) The method of claim 64, wherein the pharmaceutical ~~compounds are~~ composition is used for the inhibition of tumor growth in humans in a regimen with radiation treatment.
73. (Canceled) ~~The method of claim 64, wherein the pharmaceutical composition comprises a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, and a pharmaceutically~~

~~acceptable carrier, wherein the composition is free of the
A polymorph.~~

74. (Currently amended) A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), endometrial cancer, glioma, melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal and skin cancers, autoimmune, neoplastic cutaneous diseases or atherosclerosis in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically or pharmaceutically acceptable salts thereof in anhydrous and hydrate or hydrate forms,
- wherein the treatment further comprises,
- a) treatment with either or both anti-EGFR and anti-EGF antibodies,
 - b) administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metalloproteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, CTLA₄ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab, or
 - c) radiation treatment.
75. (Previously presented) The method of claim 15, wherein the abnormal cell growth is pancreatic cancer.
76. (Previously presented) The method of claim 15, wherein the abnormal cell growth is colorectal cancer.

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77. (Previously presented) The method of claim 15, wherein the abnormal cell growth is prostate cancer.
78. (Previously presented) The method of claim 15, wherein the abnormal cell growth is breast cancer.
79. (Previously presented) The method of claim 15, wherein the abnormal cell growth is esophageal cancer.
80. (Previously presented) The method of claim 15, wherein the abnormal cell growth is ovarian cancer.
81. (Previously presented) The method of claim 15, wherein the abnormal cell growth is glioblastoma multiforme.
82. (Previously presented) The method of claim 15, wherein the abnormal cell growth is hepatic cancer.
83. (Previously presented) The method of claim 15, wherein the abnormal cell growth is renal cancer.
84. (Previously presented) The method of claim 15, wherein the abnormal cell growth is gastric cancer.
85. (Previously presented) The method of claim 15, wherein the abnormal cell growth is bladder cancer.
86. (Previously presented) The method of claim 16, wherein the abnormal cell growth is non-small cell lung cancer (NSCLC).
87. (Previously presented) The method of claim 16, wherein the abnormal cell growth is head and neck cancer.

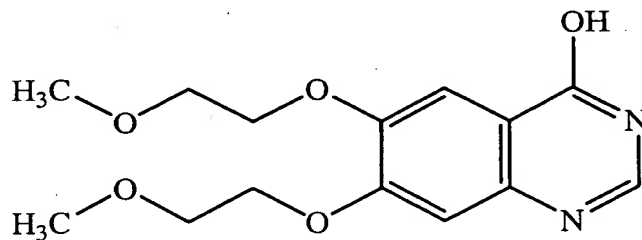
88. (Previously presented) The method of claim 64 for the treatment of non-small cell lung cancer (NSCLC).
89. (Previously presented) The method of claim 64 for the treatment of endometrial cancer.
90. (Canceled) ~~The method of claim 64 for the treatment of glioma.~~
91. (Canceled) ~~The method of claim 64 for the treatment of melanoma.~~
92. (New) A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), endometrial cancer, glioma, melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal cancers, neoplastic cutaneous diseases or atherosclerosis in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph, and a pharmaceutically acceptable carrier.
93. (New) The method of claim 92, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.
94. (New) The method of claim 92, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).

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95. (New) The method of claim 92, for use in treatment of tumors that express EGFRvIII.
96. (New) The method of claim 92, wherein the treatment further comprises a combination with any of chemotherapy and immunotherapy.
97. (New) The method of claim 92, wherein the treatment further comprises, treatment with either or both anti-EGFR and anti-EGF antibodies.
98. (New) The method of claim 92, wherein the treatment further comprises a further administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, CTLA₄ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 MAb.
99. (New) The method of claim 92, wherein the pharmaceutical compounds are used as radiation sensitizers for cancer treatment or in combination with anti-hormonal therapies.
100. (New) The method of claim 92, wherein the pharmaceutical compounds are used for the inhibition of tumor growth in humans in a regimen with radiation treatment.
101. (New) The method of claim 92 for the treatment of glioma.
102. (New) The method of claim 92 for the treatment of melanoma.
103. (New) The pharmaceutical composition of claim 58, wherein the therapeutically effective amount is from 1 to 7000 mg.

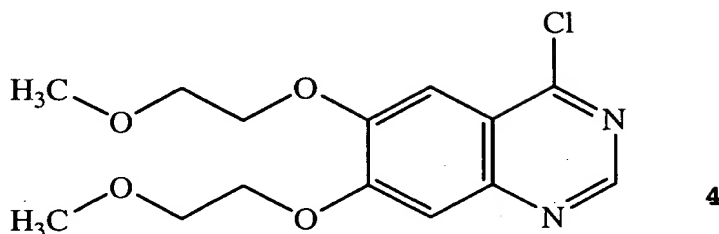
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104. (New) The pharmaceutical composition of claim 103, wherein the therapeutically effective amount is from 5 to 2500 mg.
105. (New) The pharmaceutical composition of claim 104, wherein the therapeutically effective amount is from 100 to 1600 mg.
106. (New) The pharmaceutical composition of claim 103, wherein the therapeutically effective amount is from 5 to 200 mg.
107. (New) The pharmaceutical composition of claim 106, wherein the therapeutically effective amount is from 25 to 200 mg.
108. (New) The method of claim 14, wherein the therapeutically effective amount is from 100 to 1600 mg/week.
109. (New) The method of claim 14, wherein the therapeutically effective amount of the polymorph is administered weekly.
110. (New) A process for the production of the polymorph B of claim 3 comprising the steps of:
a) substitution chlorination of a compound of formula 3



3

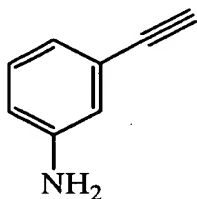
having an hydroxyl group, to provide a compound of formula 4



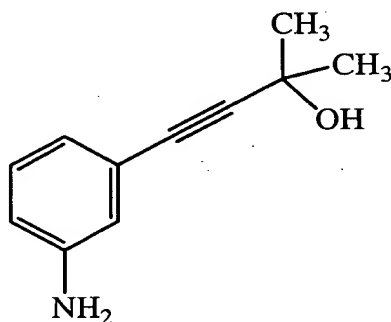
by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide;

b) quenching the substitution chlorination in the presence of aqueous sodium bicarbonate;

c) preparation of a compound of formula 6



in situ from starting material of compound of formula 5



by heating the compound of formula 5 in a suspension of metal alkali and solvent;

d) reaction of the compound of formula 6 in situ with the compound of formula 4 wherein the compound of formula 6 replaces the chlorine in the compound of formula 4 to give the N-(3-

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ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride; and

e) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in alcohol, into the polymorph B form.

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Remarks

Claims 1-7, 14-32, 50, 52-54 and 58-91 were pending in the subject application. By this amendment, applicants have canceled claims 73, 90 and 91, amended claims 26, 29, 50, 63, 64, 71, 72 and 74, and added new claims 92-110. Accordingly, claims 1-7, 14-32, 50, 52-54, 58-72, 74-89 and 92-110 are currently pending.

Support for new claims 92-102 may be found, *inter alia*, in the specification as originally filed on page 13, line 33 to page 34, line 28, and on page 24, line 9 to page 27, line 32.

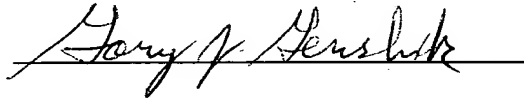
Support for new claims 103-109 may be found, *inter alia*, in the specification as originally filed on page 38, lines 9-13, and on page 50, lines 16-20.

Support for new claim 110 may be found, *inter alia*, in the specification as originally filed on page 19 and 11 to page 22, line 16.

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No fee, other than the enclosed \$374.00 fee for the extra claims, is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

A handwritten signature in cursive script, reading "Gary J. Gershik", is written over a horizontal line.

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Serial No. 09/711,272

Applicants: Timothy Norris et al.

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INFORMATION DISCLOSURE CITATION
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U.S. PATENT DOCUMENTS

| Examiner Initial | Document Number | Date | Name | Class | Subclass | Filing Date if Appropriate |
|------------------|-----------------|----------|----------------------------------|-------|-----------------|----------------------------|
| | 6 4 7 6 0 4 0 | 11/5/02 | Norris et al. (Exhibit 1); | 514 | 266.4 | |
| | 6 1 6 9 0 9 1 | 1/2/01 | Cockerill et al. (Exhibit 2); | 514 | 228.2 | |
| fm | 6 0 0 4 9 6 7 | 12/21/99 | McMahon et al. (Exhibit 3); | 514 | 266.4 | |
| TCW | 5 2 1 4 1 4 4 | 5/25/93 | Tai et al. (Exhibit 4); | 544 | 283 | |
| TCW | 4 2 8 1 1 2 7 | 7/28/81 | LeMahieu et al. (Exhibit 5); | 544 | 287 | |
| DM | 3 8 0 0 0 3 9 | 3/26/74 | Marquis et al. (Exhibit 6); | 514 | 266.1 | |
| | 9 5 5 5 5 3 4 | 7/28/99 | Allen et al. (Exhibit 7); | not | public document | |

FOREIGN PATENT DOCUMENTS

| Document Number | Date | Country | Class | Subclass | Translation |
|-------------------|---------|------------------|-------|----------|-------------|
| | | | | | Yes No |
| WO 0 1 3 4 5 7 4 | 5/17/01 | PCT (Exhibit 8); | | | |
| EP 0 8 3 7 0 6 3 | 4/22/98 | EPO (Exhibit 9); | | | |
| JP 0 6 7 3 0 2 5 | 3/15/94 | JP (Exhibit 10); | | | |
| JP 10 0 3 6 3 2 5 | 2/10/98 | JP (Exhibit 11); | | | |
| JP 10 0 3 6 3 2 6 | 2/10/98 | JP (Exhibit 12); | | | |
| JP 9 1 6 5 3 8 5 | 8/25/95 | JP (Exhibit 13); | | | |
| RU 2 1 2 7 2 6 3 | 1/15/93 | RF (Exhibit 14); | | | |
| NZ 0 2 4 5 6 6 2 | 1/15/93 | NZ (Exhibit 15); | | | |

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

Melissaris, A.P. et al., "A Simple and Economical Synthetic Route to p-Ethynylaniline and Ethynyl-Terminated Substrates" (1994) *J. Org. Chem.* 59: 5818-5821 (Exhibit 16);

Montalbert, C. et al., "A Convergent Synthesis of Functionalized B-seco Taxane Skeletons" (1995) *Tetrahedron Letters* 36(33): 5891-5894 (Exhibit 17);

Trillo et al., (1993) *Tratado de Farmacia Galencia*, Primera Edicion, pp. 81, 83, 84 (Exhibit 18); and

Sun Cunji et al., (1981) *Yaoxue Xuebao* 16(8): 564-570 C.A. 96 122727 (Exhibit 19).

EXAMINER *[Signature]* DATE CONSIDERED 5/13/04

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U.S. PATENT DOCUMENTS

| Examiner Initial | Document Number | Date | Name | Class | Subclass | Filing Date if Appropriate |
|------------------|-------------------|---------|-------------------------------|-------|----------|----------------------------|
| | 20 02 00 61 3 0 4 | 5/23/02 | Miller et al. (Exhibit 1); | | | |
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FOREIGN PATENT DOCUMENTS

| | Document Number | Date | Country | Class | Subclass | Translation | |
|----|------------------|---------|------------------|-------|----------|-------------|----|
| | | | | | | Yes | No |
| gm | WO 9 6 2 5 4 2 2 | 8/22/96 | PCT (Exhibit 2); | | | | |
| gm | WO 0 1 7 0 2 5 5 | 9/27/01 | PCT (Exhibit 3); | | | | |

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

| | |
|----|---|
| Tr | Driscoll D. et al., "Effect of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor PD183805 on Vascular Endothelial Growth Factor Secretion from Several Tumor Models" (1999) XP-001014746 (Abstract only) (Exhibit 4) |
| gm | Ishiwata T. et al., "Characterization of Keratinocyte Growth Factor and Receptor Expression in Human Pancreatic Cancer" (1998) <i>American Journal of Pathology</i> 153(1): 213-222 (Exhibit 5); |
| gm | Liu N. et al., "Comparative Phenotypic Studies of Duct Epithelial Cell Lines Derived from Normal Human Pancreas and Pancreatic Carcinoma" (1998) <i>American Journal of Pathology</i> 153(1) 263-269 (Exhibit 6); |
| Ru | Watanabe M. et al., "Overexpression of Keratinocyte Growth Factor in Cancer Cells and Enterochromaffin Cells in Human Colorectal Cancer: (2000) <i>Pathology International</i> 50:363-372 (Exhibit 7) and |
| Tr | Woodburn J.R. et al., "ZD1839, An Epidermal Growth Factor Tyrosine Kinase Inhibitor Selected for Clinical Development" (1997) XP-001009911 (Abstract only) (Exhibit 8). |
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EXAMINER

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Exhibit A

PENDING CLAIMS

1. A compound selected from the anhydrous and hydrate forms of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine mesylate.
2. A compound according to claim 1 wherein said compound is an anhydrous form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine mesylate.
3. A compound according to claim 1 wherein said compound is polymorph A characterized by the following peaks in its X-ray powder diffraction pattern

| | | | | | | | | | | |
|-------------------|------|------|------|------|------|-------|------|------|------|-------|
| Peak No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 2 θ (°) Cu | 6.3 | 7.15 | 9.8 | 13.4 | 13.7 | 18.05 | 18.9 | 19.6 | 20.0 | 21.35 |
| d space | 14.1 | 12.3 | 9.0 | 6.6 | 6.4 | 4.9 | 4.7 | 4.5 | 4.4 | 4.15 |
| Peak No. | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| 2 θ (°) Cu | 21.8 | 23.1 | 26.8 | | | | | | | |
| d space | 4.1 | 3.85 | 3.3 | | | | | | | |

4. A compound according to claim 1 wherein said compound is polymorph B characterized by the following peaks in its X-ray powder diffraction pattern

| | | | | | | | | | | |
|-------------------|------|-------|------|------|------|------|------|------|------|------|
| Peak No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 2 θ (°) Cu | 5.4 | 8.8 | 13.4 | 13.7 | 15.3 | 15.7 | 17.4 | 17.8 | 18.4 | 18.8 |
| d space | 16.3 | 10.1 | 6.6 | 6.5 | 5.8 | 5.65 | 5.1 | 5.0 | 4.8 | 4.7 |
| Peak No. | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| 2 θ (°) Cu | 19.5 | 19.85 | 20.1 | 21.1 | 21.8 | 22.6 | 24.1 | 25.2 | 25.9 | 26.7 |
| d space | 4.55 | 4.5 | 4.4 | 4.2 | 4.1 | 3.9 | 3.7 | 3.5 | 3.4 | 3.3 |
| Peak No. | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
| 2 θ (°) Cu | 28.3 | 30.9 | | | | | | | | |
| d space | 3.1 | 2.9 | | | | | | | | |

5. A compound according to claim 1 wherein said compound is polymorph C characterized by the following peaks in its X-ray powder diffraction pattern.

| | | | | | | | | | | |
|-------------------|------|-------|-------|------|-------|-------|------|-------|------|------|
| Peak No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 2 θ (°) Cu | 6.0 | 8.3 | 10.3 | 11.5 | 12.55 | 13.45 | 16.0 | 16.75 | 17.4 | 17.9 |
| d space | 14.7 | 10.6 | 8.6 | 7.7 | 7.05 | 6.6 | 5.5 | 5.3 | 5.1 | 4.95 |
| Peak No. | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| 2 θ (°) Cu | 18.1 | 18.65 | 19.35 | 20.6 | 23.0 | 24.0 | 24.8 | 26.75 | 27.2 | 36.3 |
| d space | 4.9 | 4.75 | 4.6 | 4.3 | 3.9 | 3.7 | 3.6 | 3.3 | 3.3 | 2.5 |

6. A compound according to claim 1 wherein said compound is N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine mesylate monohydrate.
7. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier wherein the hyperproliferative disorder is brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, breast cancer, head cancer, neck cancer, renal cancer, kidney cancer, ovarian cancer, prostate cancer, colorectal cancer, oesophageal cancer, gynecological cancer or thyroid cancer.
9. A method of treating a hyperproliferative disorder by inhibiting the epidermal growth factor receptor ("EGFR") in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound according to claim 1 wherein the hyperproliferative disorder treatable by inhibition of the epidermal growth factor receptor ("EGFR") is brain cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, prostate cancer, colorectal cancer, lung cancer, renal cancer, kidney cancer, ovarian

cancer, gynecological cancer or thyroid cancer.

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.
13. The pharmaceutical composition of claim 12, wherein the compound is essentially polymorph A.
14. The pharmaceutical composition of claim 12, wherein the compound is essentially polymorph B.
15. The pharmaceutical composition of claim 12, wherein the compound is essentially polymorph C.